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RETROGRADE EJACULATION RELATED INFERTILITY IN ILE-IFE, NIGERIA.

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ABSTRACT.

Background: Globally, the incidence of male infertility is on the increase[1,2]. However, the contribution of retrograde ejaculation to this increasing incidence of male infertility is not known locally.
Objectives:
1. To determine the incidence of retrograde ejaculation by using the WHO criterion among male partners of patients who were being managed for infertility at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria between 1st of February and 31st of August 2006 .
2. To determine the Retrograde-ejaculation ratio (RER) of each subject by a proposed formula as an extension of the WHO criterion.
3. To highlight the risk factors and the management options available for the treatment of retrograde ejaculation.
Subjects and methods: During the study period, 71 male partners of consecutive female patients who reported at the Infertility clinic were recruited. However, the specimens of 70 male partners were analyzed because one of them inadvertently spilled his post-ejaculatory urine specimen and consequently was excluded from the study. Prior to the collection of ejaculatory fluid and post-ejaculatory urine specimens for analysis, they were instructed to abstain from sexual intercourse for at least 3 days and to collect the first post-ejaculatory urine specimen for analysis.
The WHO criterion [1] ***states that a cloudy urine specimen with the presence of a total number of spermatozoa in urine equal to or exceeding the number of spermatozoa in semen, strongly supports the diagnosis of retrograde ejaculation.***
The sperm counts in seminal fluid and urine for each subject were determined. Thereafter, the sperm concentration in urine (SCU) and sperm concentration in seminal fluid(SCSF) were determined respectively thus: sperm count in urine/volume of urine; sperm count in seminal fluid/ volume of seminal fluid. The Retrograde ejaculation ratio (RER) was calculated thus: sperm count in urine / sperm count in seminal fluid. A questionnaire containing the bio-data and risk factors associated with retrograde ejaculation was completed for each subject.

Results: Of the 70 cases included in the analysis, 32(45.7%) had primary infertility while 38(54.3%) had secondary infertility. The age range was 28-65(mean for primary and secondary infertility were 36 and 42.1 respectively) years. The duration of infertility ranged from 1-16 years (mean4± 2.92). Based on the WHO criterion previously stated, only 1/70(1.42%) of the cases was positive with a retrograde ejaculatory ratio (RER) of infinity as he had azoospermia. This was in a 47 year old man with secondary infertility who had no identifiable risk factor prior to the study.
There were 8/70(11.42%) of the cases studied with azoospermia but only 1/8 (12.5%) of those azoospermic had retrograde ejaculation.

Conclusion: To make a diagnosis of male factor infertility, semen analysis remains the cornerstone of all the laboratory assays. However, to make a categorical diagnosis of retrograde ejaculation, **focused laboratory testing** is imperative. The incidence of retrograde ejaculation appeared low

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(1.42%) in our environment but this is in consonance with studies elsewhere. It is strongly advisable that cases of azoospermia and severe oligozoospermia be screened for retrograde ejaculation as there are many modalities of therapy to aid the affected males fulfil their wishes of becoming fathers. Lastly, when the retrograde ejaculation ratio (RER) is ≥ 1 with the presence of a cloudy urine, the diagnosis is highly probable.

Key words: Retrograde ejaculation, azoospermia, male infertility.

Table 1: Showing the retrograde ejaculation ratio and appearance of urine of subjects.

S/No	AGE (Years)	Type of Infertility	Duration of Infertility (Years)	SCSF= TSSF* / VOL OF SEMINAL FLUID	SCU= TSU*/ VOL OF URINE (millins/ml)	RER = SCU/ SCSF	Appearance of Urine
1	44	Secondary	12	5.6/6=0.94	0/1=0	0	NC
2	30	Secondary	11	0/5=0	0/15=0	0	NC
3	38	Primary	5	4.8/3=1.6	0/20=0	0	NC
4	49	Secondary	3	153/3=51	1.3/25=0.052	0.052/51=0.001	NC
5	41	Secondary	5	16.8/3=5.6	0.2/25=0.008	0.008/5.6= 0.001	NC
6	53	Secondary	3	7.5/3=2.5	0.2/25=0.008	0.008/2.5=0.0032	NC
7	36	Primary	3	7.6/4=1.9	0/10=0	0/1.9=0	NC
8	30	Secondary	6	0.4/2= 0.2	0/15=0	0/0.2=0	NC
9	30	Secondary	4	15/3=5.0	0/10=0	0/5=0	NC
10	40	Secondary	1	8.4/6=1.4	0.2/20= 0.01	0.01/1.4=0.005	NC
11	35	Primary	2	1.5/3=0.5	0/20=0	0/0.5 =0	NC
12	38	Secondary	4	2.4/2=1.2	0.1/20=0.005	0.005/1.2=0.004	NC
13	30	Secondary	5	22/2=11	0.1/18=0.005	0.005/11=0.005	NC
14	33	Primary	1.5	105/5=21	0.2/30=0.006	0.00028	NC
15	34	Secondary	3	.5/5=0.1	0/20=0	0/0.1=0	NC
16	34	Primary	4	6.5/5=1.3	0.1/10 =0.01	0.01/1.3=0.007	C
17	47	Secondary	2	0/3=0	0.9/25=0.03	0.03/0=Infinity	C**
18	42	Secondary	2	1.4/2=0.7	0.1/25=0.004	0.004/0.7=0.005	NC
19	34	Primary	1	54/2=27	2.9/15=0.193	0.193/27=0.007	C
20	32	Secondary	3	84/3=28	0.1/15=0.006	0.006/28=0.002	NC
21	31	Primary	1.5	69/3=23	0.5/30=0.016	0.016/23=0.0007	NC
22	31	Secondary	1	46/10=4.6	0/25=0	0/4.6=0	NC
23	42	Secondary	9	0.5/5=0.1	.1/3=0.033	0.033/0.1=0.33	NC
24	37	Secondary	8	144/4=36	0.5/2=0.25	0.25/36=0.007	C
25	40	Primary	2	345/3=105	1.7/15=0.113	0.113/105=0.001	C
26	43	Secondary	4	4.6/2=2.3	0.2/30=0.006	0.006/2.3=0.002	NC
27	34	Secondary	1	0.5/5=0.1	0.1/20= 0.005	0.005/0.1=0.05	NC
28	32	Secondary	2	18/3=6.0	0.1/10=0.01	0.01/6=0.001	NC
29	60	Secondary	8	66/3=22.0	0.3/20 = 0.015	0.015/22=0.006	NC
30 *	42	Secondary	4	9.6/4=2.4	0.1/10 =0.001	0.001/2.4= 0.0004	NC
31	38	Primary	2	375/5= 75	0.4/20= 0.02	0.02/75= 0.0002	NC
32	32	Primary	4	7.2/2=3.6	0/15=0	0/3.6=0	NC
33	35	Primary	8	22/1 =22	1.3/30= 0.04	0.04/22= 0.001	NC
34	41	Secondary	3	28/2 =14	0.1/20 = 0.005	0.005/14 =0.0003	C
35	29	Primary	2	0/0.5 =0	0/15=0	0/0=0	NC
36	35	Primary	4	14/1 =14	0.6/15= 0.04	0.04/14= 0.002	C
37	38	Primary	1	90/3=30	3.3/15 =0.22	0.22/30= 0.007	NC
38	45	Secondary	2	4/1=4	0/25=0	0/4=0	NC
39	53	Secondary	3	75/3=25	0.1/15=0.006	0.006/25 =0.0002	NC
40	37	Secondary	3	90/2=45	0.2/20= 0.01	0,01/45=0.0002	NC
41	41	Secondary	3	24/6=4	0.1/15=0.0004	0.0004/4= 0.0001	NC
42	40	Secondary	2	120/1=120	60/15=4	4/120= 0.03	C
43	28	Primary	1	175/5=35	1/25= 0.04	0.04/35 = 0.001	NC
44	46	Secondary	16	128/8 =16	0.1/25 =0.004	0.004/16= 0.00025	NC
45	39	Primary	6	360/3=120	0/3=0	0/120=0	NC
46	65	Secondary	1	70/1=70	0.1/30 =0.003	0.003/70=0.0000 4	NC
47	57	Secondary	8	28/2 =14	1.5/10=0.15	0.15/140.01	NC
48	32	Primary	2	60/1=60	1.5/25=0.06	0.06/60=0,01	NC
49	42	Secondary	4	30/2=15	0.1/25=0.004	0.004/15= 0.0002	NC
50	30	Primary	2	90/1=90	8.6/25=0.34	0.34/90=0.003	NC
51	36	Secondary	3	6/3=2	0.1/20=0.005	0.005/2=0.0025	NC
*52	35	Primary	1	46/2=23	3/5=0.6	0.6/23=0.026	NC
53	39	Primary	2	0.4/4=0.1	0.2/20=0.01	0.01/0.1=0.09	NC
54	39	Primary	1	290/10=29	75/25=3	3/29=0.1	C
55	36	Primary	7	60/4=15	0.1/25=0.04	0.04/15=0.0026	NC
56	60	Secondary	5	285/3=85	0/25=0	0/85=0	NC
57	39	Primary	8	0/2=0	0/15=0	0/0=0	NC
58	42	Primary	4	4/2=2.0	0.1/25=0.002	0.002/2=0.001	NC
59	34	Primary	1	72/6=12	0.1/16=0.006	0.006/12=0.0005	NC
60	35	Primary	3	70/5=14	0.1/20=0.005	0.005/14=0.0003	NC
61	32	Primary	5	12/1=12	0.5/15=0.03	0.03/12=0.0025	NC
62	39	Primary	4	62/2=31	2.5/30=0.008	0.008/31=0.0002	NC
63	42	Primary	4	20/4=5	0.3/20=0.015	0.015/5=0.003	NC
64	41	Secondary	3	16/4=4	0.3/15=0.02	0.02/4=0.005	NC
65	40	Primary	5	138/6=23	0.4/6=0.06	0.06/23=0.002	NC
66	38	Secondary	4	140/5=28	0.6/15=0.04	0.04/28=0.001	NC
*67	45	Primary	11	85/5=17	0/20=0	0/17=0	NC
68	46	Secondary	1	60/4=15	0.3/10=0.03	0.03/15=0.002	C
*69	50	Secondary	6	8/2=4	0/10=0	0/4=0	NC
70	38	Primary	4	0.6/3	0/25=0	0/3=0	NC

SCSF= Sperm concentration in seminal fluid; TSSF=Total sperm in seminal fluid ; SCU= Sperm concentration in urine; TSU = Total sperm in urine; RER= Retrograde ejaculation Ratio; NC= Not Cloudy; C= Cloudy;

* = Risk factor present(previous administration of antihypertensives, psychotropics, medical diseases like diabetes mellitus, multiple sclerosis and pelvic surgeries like prostatectomy).

**=Retrograde ejaculation positive.

Table: 2 showing the range of variables and there mean values.

Variables	Minimum	Maximum	Mean	SD
Duration of Infertility(Years)	1	16	4	$\pm$2.972
Total sperm in seminal fluid(millions)	0.0	375	61.97	$\pm$ 87.415
Volume of seminal fluid (ml)	0.5	10	3.38	$\pm$1.965
Total sperm in urine (millions)	0.0	75	2.43	$\pm$11.294
Volume of urine(ml)	1.0	30	18.16	$\pm$7.356
Sperm concentration in seminal fluid(millions/ml)	0.000	120	21.84	$\pm$ 29.942
Sperm concentration in urine(millions/ml)	0.000	4	0.14	$\pm$0.590
Retrograde Ejaculation Ratio	0.00	Infinity	Indeterminable	—=

Table 3 showing the statistical significance of variables.

Variables	Mean		SD		t		df		P-value	
	Primary	Secondary	Primary	Secondary	Primary	Secondary	Primary	Secondary	Primary	Secondary
Total sperm in seminal fluid(millions)	82.7	45.2	± 109.3	± 61.25	1.80	1.72	68	46.8	0.07	0.091
Volume of seminal fluid(ml)	3.32	3.500	± 1.99	± 1.92	- 0.36	-0.36	68	65.12	0.71	0.71
Total sperm in urine(millions)	3.26	1.79	± 13.2	± 9.70	0.53	0.52	68	55.93	0.59	0.60
Volume of urine (ml)	18.9	17.73	± 7.32	± 7.41	0.66	0.66	68	66.25	0.51	0.51
Sperm concentration in seminal fluid(millions/ml)	25.7	17.26	± 32.1	± 27.02	1.20	1.18	68	60.77	0.23	0.24
Sperm concentration in urine(millions/ml)	0.15	0.12	± 0.53	± 0.64	0.20	0.20	68	67.98	0.83	0.83
Age (years)	36.0	42.1	±3.99	±8.97	- 3.54	-3.75	68	52.93	0.001	0.000

Table 4: Appearance of Urine.

Appearance	Type of Infertility	
	Primary	Secondary
Cloudy	5 (15.6%)	5 (13.2%)
Not Cloudy	27 (84.4%)	33 (86.8%)
Total	32 (100.0)	38 (100.0)
$X^2 = 0.086$, df = 1, P-value = 0.769		

DISCUSSION

Retrograde ejaculation (RE), an ejaculatory dysfunction, is defined as misdirected propulsion of semen from the posterior urethra into the bladder. The condition can either be complete (total absence of ejaculation) or incomplete (minimal antegrade emission).

Antegrade ejaculation through the urethral meatus is achieved through coordinated activity of the autonomic nervous system; contraction of the posterior urethra with closure of the bladder neck is effected by the sympathetic system and contraction of the bulbocavernous and ischiocavernous muscles is by the parasympathetic system coupled with generalized pelvic floor activity. Any slight interference in these highly coordinated series of events may result in abnormal activity of the internal sphincter of the bladder neck and cause retrograde ejaculation. Thus the cause of RE may be anatomical, traumatic, iatrogenic, neurogenic, drug induced or idiopathic[3,16,17,18].

RE has been reported to be the cause of male infertility in 0.3 – 2% of cases investigated[4,5] .In this study, the incidence was 1/70(1.42%) among the cohort of men investigated(Table 1). From this same table, 8/70 (11.42%) had azoospermia and 1/8 (12.5%) of these azoospermic cases had retrograde ejaculation.

In this study, only 4 of the cases had risk factors predisposing to the development of RE. These were previous pelvic surgery(specific nature could not be ascertained from the patient), spina bifida and syringomyelia, diabetes mellitus, prostate enlargement with lower urinary tract symptoms medicated with alpha-adrenergic blockers such as tamsulosin and the same patient later had prostate surgery. However, none of these four cases developed RE. Interestingly, the only patient that was diagnosed to have RE during the study never had any identifiable risk factor in his medical history but after semen analysis, was identified to have azoospermia (Table 1).

Diagnostic clues to the presence of RE include absent or intermittent emission of semen, orgasm without ejaculation, and presence of spermatozoa and fructose in post-coital urine specimens[3]. Urine cloudiness or turbidity after ejaculation due to the presence of semen in urine is suggestive but not confirmatory of RE. Table 4 shows that the appearance of urine was not statistically significant (X^2=0.086, df=1, p value =0.769). Ariagno et al[6], opined that mere presence of sperm in the post-masturbatory urine is not adequate in making the diagnosis of RE but total sperm in urine (> $3.8x\ 10^6$) and semen volume added to their proposed retrograde ejaculation index(> 2.16%) may identify true retro-ejaculatory patients. Another criterion for diagnosing RE, is identification of more than 5-10 sperm per high power field in the post-ejaculatory urine specimen[7].Other criteria used for the diagnosis include a sperm count in the post-ejaculate urine greater than 5 million or post-ejaculate urine with more than 5% to 10% of the ejaculated sperm[3].

In Table 1, there were 10/70 (14.3%) of the subjects with cloudy post-ejaculatory urine but only one of these had a total sperm count in urine greater than

total number of spermatozoa in semen which is the basis for the WHO criterion for the diagnosis of RE[1]. Thus, the incidence of RE during the study period was found to be 1/70 (1.42%) which is in consonance with findings from other studies with incidence ranging from 0.3-2%[4,5].

Table 3 shows that the age of the subjects included in the study was the only variable that was statistically significant (p value=0.000).

Table 2 shows that the duration of infertility among the subjects ranged from 1-16 years (mean= 4±2.972).In the same table, the **retrograde ejaculation ratio (RER**) ranged from zero to infinity. We propose the usage of the RER (sperm concentration in urine [SCU] / sperm concentration in seminal fluid [SCSF}as an extension of the previously stated WHO criterion for the diagnosis of RE. Thus, it is highly probable that if the RER ≥1.0, with the sperm count in urine ≥ sperm count in seminal fluid with a cloudy post-ejaculatory urine specimen, there is **true retrograde ejaculation**.

Without **focused laboratory testing** as stated earlier, the diagnosis of RE will be missed and this will be highly unfortunate for the patient as several therapeutic approaches are now available. The management goal for RE-related infertility is either to

promote spontaneous antegrade ejaculation for spontaneous conception or to provide sufficient amount of motile sperm for artificial reproductive technology (ART)[3].

Management modalities for RE can be categorized into three: 1) medical management, 2) sperm retrieval from urine, and 3) surgical procedures.

Medical management of RE is based on either increasing sympathetic tone of the bladder neck or decreasing parasympathetic activity. Medical management allows for the possibility of natural conception therefore it is the first choice of therapy for RE.

Kamischke and Nieschlag reported in a meta-analysis about the usage of alpha adrenergic agonists, anti-cholinergics and anti-histaminics among 253 patients. 133/253 (53%) of these patients were able to achieve antegrade ejaculation induced either alone or in combination of these pharmacological agents.[9]. Spontaneous pregnancy was achieved in the partners of 33% of RE patients who had intercourse while on the medications.

Imipramine is the most frequently used medication for the treatment of RE, followed by midodrine and ephedrine. Imipramine has been reported to provide a 64.5% (78/121patients) rate of antegrade ejaculation and a 39.5% (30/76 patients) of spontaneous pregnancy[9]. Imipramine is considered the first- line therapy for the treatment of RE and may be administered at a dose regimen ranging from 25-75 mg /day orally. Midodrine and ephedrine have been reported to have poorer rates of inducing antegrade ejaculation and spontaneous pregnancy[10]. However, side effects like dizziness, nausea, sleep disturbances, weakness, dry mouth and restlessness may be experienced while on these pharmacological agents.

Sperm recovery from antegrade urine is the next treatment modality for RE if there is failure of medical therapy. Thus, spermatozoa can be recovered from the bladder or voided post-ejaculatory urine. The pH of fresh ejaculate ranges from 7.2 – 8.2, and osmolarity ranges from 300-380 mOsm/L[11].Any changes in pH or osmolarity, as well as bacterial contamination, can affect sperm motility and viability. The acidity and high osmolarity of urine normally causes immobilization of spermatozoa and considerable ultrastructural changes , including damage to the sperm head/mid-piece, hypo-osmotic swelling and or loss of plasma membrane[12]. Two methods have been described to recover sperm from the bladder or post-ejaculatory urine. In the first method, the urine is drained by a catheter and replaced with a 20-30 mL isotonic, sperm friendly buffer solution. After masturbation, the patient voids or is re-catheterised to recover the sperm suspension for swim-up and intrauterine insemination. The second method which is less invasive involves neutralization of the acid pH of urine by the ingestion of alkalinizing agents like sodium bicarbonate (3-5 g in 250 ml of water the morning of the procedure). Post-ejaculation, the patient provides a urine sample for evaluation of sperm count, motility,

pH and osmolarity. Spermatozoa recovered are subjected to 30mL of buffered medium like Ham's F-10. The urine sample is aliquoted into 5mL volumes and centrifuged for 10 minutes at 250g at room temperature[13].Spermatozoa recovered from men with RE are usually fragile and should be carefully handled. The presence of debris and bacterial contamination in the recovered sperm can be overcome by the addition of antibiotics to the medium and removal of the debris can be done by

precipitation or swim –up techniques[14].

Surgical treatment of RE is rarely employed in current clinical practice because medical management has been reported to be successful in more than half of the patients and sperm recovery can be successfully employed for artificial reproductive technology (ART)[3].

RE is a recognized cause of male-factor infertility even though the incidence appears to be low. The condition should be suspected in men with azoospermia, absence of antegrade ejaculation and cloudy post-ejaculatory urine and confirmation obtained with focused laboratory testing. It will be highly unfortunate if health-care workers who take care of infertile/subfertile couples miss the diagnosis of RE while evaluating them because the condition is largely amenable to treatment. In the cohort of azoospermic men, there should be a high index of suspicion for RE and with focused laboratory testing the diagnosis can be established and appropriate treatment modality instituted. Lastly, in view of the global burden of subfertility and infertility, efforts are required to make assisted reproduction more effective, less burdensome and more equally accessible.[15]

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